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Microarray Analysis of the Toxicogenomics and the Genotoxic Potential of a Cationic Lipid-Based Gene Delivery Nanosystem in Human Alveolar Epithelial A549 Cells

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ABSTRACT Viral and nonviral vectors have been widely used in gene therapy as delivery reagents for nucleic acids. Toxicity with viral vectors has increasingly led to the search for suitable nonviral vectors, such as cationic lipids/polymers, as potentially safer alternatives. However, little is known about the genomic toxicity of these delivery systems in target cells/tissues. In the current investigation, we report on the toxicogenomics and genotoxicity of cationic lipid Oligofectamine (OF) nanosystems in human alveolar epithelial A549 cells. To investigate the nature and the ontology of the gene expression changes in A549 cells upon treatment with OF nanoliposomes, microarray gene expression profiling methodology was utilized. For microarray analysis, cyanine (Cy3/Cy5)-labeled cDNA samples from treated and untreated cells were hybridized on target arrays housing 200 genes. Both OF and OF-DNA lipoplex induced significant gene expression changes belonging to the different genomic ontologies such as cell defense and apoptosis pathways. Flow cytometry analyses revealed induction of apoptosis in A549 cells treated with these nanosystems that is likely due to interactions and/or deterioration of the cell membranes. However, no DNA damage was detected by the Comet assay. These data suggest that cationic nanoliposomes in the absence of direct DNA damage elicit multiple gene expression changes in A549 cells that may compromise the main goals of gene medicine where only therapy-defined gene changes are required.

KEYWORDS Gene Delivery; Liposome; Gene Expression; Gene Therapy; Genocompatibility; Microarray; Nanosystem; Toxicogenomics

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INTRODUCTION

Gene-based therapies such as antisense oligonucleotides, ribozymes, DNAzymes, and RNA interference confer promising therapeutic paradigms for treating genetic diseases in the postgenomic era (Akhtar and Benter 2007a; Akhtar et al. 2000; Hughes et al. 2001). To correct the genetic disorders, genome-based therapeutics need to be successfully delivered to target sites using appropriate gene delivery carriers such as viral or nonviral vectors. Accordingly, a gene delivery system should possess appropriate physicochemical characteristics to pass through the biological membranes/barriers and transfer the genomedicine to target sites with minimal impacts on the integrity of target cells/tissues (Forrest and Pack 2002). These issues are primarily important for both ex vivo